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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,360	03/20/2001	Michael S. German	UCSF-129CIP	2345

7590 09/04/2003

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/817,360	Applicant(s) GERMAN, MICHAEL S.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-16,18-23,25 and 27-36* is/are pending in the application.

4a) Of the above claim(s) *14-16,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,18-21,25 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *16 June 2003* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Claims 12-16, 18-23, 25, 27-36 are pending.

Applicant's traversal, the Declaration by Dr. German filed under 1.132, the cancellation of claims 1-11, 17, 24, and 26, the addition of claims 31-36, and the amendment to claims 12, 18, 19, 25, 27, 28, and 29 in paper no. 15 filed on 6/16/03 is acknowledged and considered.

The international search report has been considered.

Election/Restrictions

This application contains claims 14-16, 22, 23, 32, 33, 35, and 36 drawn to a nonelected species without traverse in Paper No. 8.

Drawings

New corrected drawings are required in this application for the reasons set forth in the PTO-948. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

The petition for color drawings filed on 3/20/01 is acknowledged and **GRANTED**.

Claim Objections

Claims 12 and 19 are objected to because of the following informalities: the word "neuroendocrine" is misspelled in the claims. Appropriate correction is required.

Claims 32, 33, 35 and 36 are objected to because of the following informalities: the claims read on non-elected species. Appropriate correction is required.

Applicant is advised that should claim 12 be found allowable, claim 31 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should claim 19 be found allowable, claim 34 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

Applicant's arguments, see paper no. 13, filed on 6/16/03, with respect to the 112 first paragraph rejection written description have been fully considered and are persuasive. The rejection of claims 12, 18, 19, 20, and 28-30 has been withdrawn because of the amendment to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 18-20, and 28-30 remain and claims 13, 21, 31, 32, 33, 34, 35, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a nucleic acid encoding the neuroendocrine bHLH transcription factor neurogenin3 operably linked to a promoter to produce insulin-producing cell from a mammalian pancreatic cell *in vitro*, does not reasonably provide enablement for the full scope of the claimed invention (using a genus of bHLH transcription factors to differentiate a cell into any type of insulin-producing cell). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to producing insulin-producing cells *in vitro* and using the cells in a method for producing insulin in a mammalian subject. The field of the invention lies in differentiating cells into insulin producing cells using a nucleic acid molecule comprising a bHLH transcription factor.

The state of art at the time the application was filed and currently teaches that, "a number of transcription factors have been shown to control pancreas morphogenesis or the differentiation

of the endocrine cells...Although no transcription factor has been identified thus far that selectively controls β-cell formation" (IDS, Schwitzgebel et al. Development, 127:5533-5540, 2000). Furthermore, research indicates that multiple factors are required for the various steps of pancreatic cytodifferentiation. The identification of the transcription factors required for differentiation will help in understanding the timing and ultimately the signals that induce differentiation (IDS, Sander et al., J. Mol. Med. 75:327-340, 1997).

Thus, in view of the state of the art at the time the application was filed and currently, using a genus of nucleic acid molecules encoding a bHLH transcription factor for producing any type of insulin-producing cell *in vitro* is considered unpredictable.

The specification provides examples that will be briefly discussed herein:

Examples 1-3 are directed to isolation and production of the murine and human Ngn. Examples 4 and 15 are directed to constructing a vector encoding the murine Ngn3. Example 5 displays the induction of insulin in normal adult rats by treatment with the vector from Example 4. Examples 6, 16, and 17 display or contemplate the normalization of blood glucose levels in diabetic induced adult rats using the vector from 4 or 15. Example 7 is directed to overexpression of Ngn3 in transgenic mice. Example 8 is directed to the islet cell production in NeuroD1 transgenic mice. Examples 9 and 10 contemplate the construction of adenovirus vector comprising the human or mouse neuorD1 coding sequence or ACL1/ASH1 coding sequence and example 11 and 12 contemplate using either vector to induce the formation of insulin producing beta cells in normal adult rats. Examples 13 and 14 contemplate production of insulin in diabetic induced adult rats by the introduction of DNA encoding either neuorD1 coding sequence or ACL1/ASH1 coding sequence. Example 18 contemplates induction of the formation of islet cell

in vitro. Example 19 contemplates delivery of Ngn3 to human subjects. Example 20 is characterization of the Ngn3 promoter.

The claimed invention encompasses "a method for producing an insulin-producing cell *in vitro*, the method comprising introducing a nucleic acid molecule into a cell *in vitro*, the nucleic acid molecule encoding a neuroendocrine bHLH transcription factor, said introducing being in an amount sufficient for production of the bHLH transcription factor and production of insulin-producing cells. In view of the In re Wands Factors, the claimed invention is only enabled for an *in vitro* method of producing insulin-producing cells using a nucleic acid molecule encoding a bHLH transcription factor neurogenin3 and not the full scope of the claimed invention. The breadth of the claimed genus of nucleic acid molecules encoding a neuroendocrine bHLH transcription factor is not considered enabled because the specification does not disclose how to make and use a representative number of species of bHLH transcription factors for one skilled in the art to practice the full scope of the claimed methods. The as-filed specification contemplates using several types of bHLH transcription factors and only provides sufficient guidance or factual evidence for one skilled in the art to use a transcription factor, neurogenin3, for making insulin-producing cells. The art of record teaches that number of bHLH transcription factors embraced by the claimed methods is enormous. The specification does not disclose how using ngn3 to produce insulin-producing cells in vitro reasonably correlates to using a genus of neuroendocrine class b bHLH transcription factor to produce insulin-producing cells *in vitro*. Anderson further supports the unpredictability of using a genus of nucleic acid molecules encoding a bHLH transcription factor for producing insulin-producing cell *in vitro*. Anderson teaches that, "there are determination and differentiation bHLH factors and the bHLH

transcription factors may differ in only in time and place of their expression, or in the downstream genes they regulate. On the other hand, they may possess intrinsic functional differences that have so far escaped detection (US patent 6,566,496, column 19)." In addition, Anderson teaches that, "only ngn3 expression was detected and not ngn2 or ngn1 in islet cell specific genes and while our data do not directly demonstrate co-expression of these two genes in the same cells, by analogy to the nervous system it seems likely that ngn3 functions upstream of neuroD in a cascade controlling islet development (column 25)." The specification does not disclose which neuroendocrine bHLH transcription factors are involved in differentiation and determination of insulin-producing cells. The specification and the art of record do not disclose which neuroendocrine bHLH transcription factors are in the same pathway as Ngn3. The art of record teaches that HIF-1 is a bHLH transcription factor that does not produce insulin-producing cells and HIF-1 is produced in response to hypoxia.

Furthermore, with respect to claims 12, 13, 18, 19, 21, 28, 29, and 31-36 directed to producing insulin producing cells using either a precursor cell or a mammalian cell, the full scope of the claimed methods is not considered enabled. The specification teaches one skilled in the art how to use mammalian pancreatic cells in the claimed method. However, the breadth of the term "precursor cell" or "mammalian cell" embraces an enormous number of cells (stem cell, myoblast, brain cells, liver cells, cardiac cells, lung cells, etc.) and the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to reasonably extrapolate from using mammalian pancreatic cells to the any other type of cell. The specification and art of record do not teach using cells other than mammalian pancreatic cells for producing insulin. The state of the art teaches that HNF-alpha and Ngn3 are critical for

activating PAX4, which controls the formation of insulin-producing beta cells (Smith et al, JBC, 2003, pages 1-25). The specification does not teach which cells have PAX4 and HNF-alpha other than mammalian pancreatic cells. The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the reasons set forth above for producing insulin-producing cells using any type of cell other than mammalian pancreatic cells, for those skilled in the art to experiment with any type of cell so as to provide insulin-producing cells as intended by the as-filed specification at the time the invention was made. Thus, in view of the In re Wands Factors the full scope of the claims is not considered enabled.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable an *in vitro* method of producing insulin-producing cells using a nucleic acid molecule encoding a bHLH transcription factor neurogenin3 and not the full scope of the claimed invention. Given that differentiating any type of cell into specific insulin-producing cells was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a genus of bHLH transcription factors cited in the claims, one skilled in the art would have to

engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of differentiating cells into a specific type of cell.

Applicant's arguments filed 6/16/03 have been fully considered and are found partially persuasive.

Applicant's arguments with respect to correlating in vivo results to in vitro results have been fully considered and they are found partially persuasive because the Declaration by Dr. German teaches a method for producing insulin-producing cells in vitro comprising introducing a nucleic acid encoding Ngn3 into mPAC cells in vitro resulting in insulin production in said cells.

However, the argument with respect to correlating in vivo results to in vitro results are not found persuasive for enabling the full scope of the claimed invention because in view of the In Re Wands Factors, the specification fails to teach one skilled in the art how to produce insulin-producing cells *in vitro* using a genus of neuroendocrine class B bHLH transcription factors.

Furthermore, with respect to the argument that the experiments cited in the Declaration by Dr. German under 1.132, teaches three neuroendocrine bHLH transcription factors neurogenin3, neuroD1 and mash1 that sufficiently enables the genus of bHLH transcription factors to make insulin producing cells *in vitro*, the argument is not found persuasive.

Appendixes A-C of the Declaration teach that neuroD and ngn3 produce insulin in mPAC cells *in vitro* using the claimed methods. However, Appendix A and C do not display that myoD and Mash1 produced insulin in the mPAC cells. Thus, Appendix A supports the unpredictability of correlating the results produced by two bHLH transcription factors to a genus of bHLH

transcription factors. The art of record teaches that number of bHLH transcription factors embraced by the claimed methods is enormous. The specification does not disclose how using ngn3 to produce insulin-producing cells *in vitro* reasonably correlates to using a genus of neuroendocrine class B bHLH transcription factor to produce insulin-producing cells *in vitro*. Anderson further supports the unpredictability of using a genus of nucleic acid molecules encoding a bHLH transcription factor for producing insulin-producing cell *in vitro*. Anderson teaches that, "there are determination and differentiation bHLH factors and the bHLH transcription factors may differ in only in time and place of their expression, or in the downstream genes they regulate. On the other hand, they may possess intrinsic functional differences that have so far escaped detection (US patent 6,566,496, column 19)." In addition, Anderson teaches that, "only ngn3 expression was detected and not ngn2 or ngn1 in islet cell specific genes and while our data do not directly demonstrate co-expression of these two genes in the same cells, by analogy to the nervous system it seems likely that ngn3 functions upstream of neuroD in a cascade controlling islet development (column 25)." The specification does not disclose which neuroendocrine bHLH transcription factors are involved in differentiation and determination of insulin-producing cells. The specification and the art of record do not disclose which neuroendocrine bHLH transcription factors are in the same pathway as Ngn3. The art of record teaches that HIF-1 is a bHLH transcription factor that does not produce insulin-producing cells and HIF-1 is produced in response to hypoxia.

Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using a genus of neuroendocrine class b bHLH transcription factors to produce insulin producing cells in vitro, for those skilled in the art to experiment with neuroendocrine bHLH transcription factors so as to provide insulin-producing cells as intended by the as-filed specification at the time the invention was made. See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for which bHLH transcription factors are operable or inoperable for producing insulin-producing cells *in vitro*, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the specification to the full breadth of the claimed invention. Therefore, in view of the In re Wands Factors, it would take one skilled in the art an undue amount of experimentation to practice the full scope of the claimed invention.

In addition, with respect to the argument that "since phylogenectically closely related transcription factor typically have similar function (See for example Lee Curr. Opin. Neurobiol

7:13-20 and Jan et al.75:827-830)", the argument is not found persuasive because neither articles was enclosed with the applicant's response. Instead, two articles (Levy Gene 54: 167-173, 1987 and Hiraiwa, Gene 193-199, 1988) were submitted. These articles were not considered because neither article supports the claimed invention.

The Declaration by Dr. German under 37 CFR 1.132 filed on 6/16/03 is insufficient to overcome the rejection of claims based upon 112 enablement as set forth in the last Office action for same reasons as set forth above.

Applicant's arguments, see paper no. 13, filed on 6/16/03, with respect to the 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 19 and 25 has been withdrawn because of the amendment to the claims. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claim 12.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 12, 13, 21, 25, 30, 31, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 13 recite the limitation "the islet transcription factor". There is insufficient antecedent basis for this limitation in the claims.

Claim 21 recites the limitation "the islet transcription factor". There is insufficient antecedent basis for this limitation in the claim.

Claims 25 and 30 are vague and indefinite because of the phrase "a nucleic acid molecule operably linked to a promoter, a nucleic acid molecule encoding neurogenin3 (Ngn3)". In view of the phrase, it is unclear if one or two different nucleic acids are being introduced into the cell in vitro.

Claim 31 recites the limitation "said bHLH islet transcription factor". There is insufficient antecedent basis for this limitation in the claim.

Claim 34 recites the limitation "said bHLH islet transcription factor". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

Applicant's arguments, see paper no. 13, filed on 6/16/03, with respect to the 102(e) rejections have been fully considered and are persuasive. The rejections of Claims 12, 18, 19, 20, 28, 29, and 30 has been withdrawn because of the amendment to the claims.

Conclusion

There is no prior art on the elected species Ngn3 and there are no allowable generic or linking claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER